ICTMM2016 Travel Medicine Oceania Workshop

Current state of malaria and its prophylaxis

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Overview

- How is malaria travelling globally?
- Have we made progress towards control?
- What’s in a name?
  - The species of malaria that affect humans &
  - The malaria life cycle
- How does malaria present?
- What’s new in malaria treatment?
- What’s new in malaria prophylaxis?
- How else do we prevent malaria?

How is malaria travelling globally?

WHERE
95 countries with malaria transmission
  • at risk 3.2 billion persons = half of world population
MORBIDITY
  • 214 million clinical cases/yr; about 90% in sub-Saharan Africa
MORTALITY
  • 438,000 deaths; about 90% in Sub-Saharan Africa


http://www.plosmedicine.org/lookup/doi/10.1371/journal.pmed.0040001
Global Age – Sex distribution of Malaria Deaths in 2013


Have we made progress towards control?

Past and Projected Funding for Malaria Control 2000 - 2016

An Historical Achievement? Nearly All Countries Could Converge by 2035

Have we made progress towards control?

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Global, malaria death rates reduced by 60%
Globally, rate of new cases in populations at risk reduced by 37%

Have we made progress towards control?

Globally, malaria death rates reduced by 60%
Globally, rate of new cases in populations at risk reduced by 37%

We are striking back against malaria!!!
What's in a name? The species of malaria

Traditionally, we talk about four (4) main species of malaria:
- *P. falciparum* ("malignant")
- *P. vivax* ("benign")
- *P. malariae*
- *P. ovale*

But need to add a discussion of *P. knowlesi*:
- *P. knowlesi* – the "5th species" of malaria
- Other sub-genera affecting different animals

**Key Ref:** Daneshvar C, et al. Clinical and laboratory features of human *P. knowlesi* infection. CID 2009; 49: 852-860 - "5th" species

- *Plasmodium knowlesi*, discovered in 1931, is increasingly being recognized as a cause of human malaria in Southeast Asia.
- Reservoir is primates, but also infects humans
- In a systematic study of the presentation and course of patients with acute *P. knowlesi* infection
  - Knowlesi malaria causes a wide spectrum of disease.
  - Most cases are uncomplicated and respond promptly to treatment, but approximately 1 in 10 patients develop potentially fatal complications.

Malaria species reported Australia 2014

Malaria notifications in Australia
Life cycle of malaria

How long does it take to infect the liver?
30-60 min

How long does it take for the parasites to start infecting blood cells giving rise to symptoms of malaria?
About 7-30 days

May lead to misdiagnosis

- Fever, rigors → Influenza, typhoid, UTI, tick-bite fever, trypanosomiasis
- Jaundice → Hepatitis
- Mental state ↓ → Meningitis
- Diarrhoea → Travellers’ diarrhoea
- Multi-organ failure → Septicaemia

Malaria is a great mimicker

How does malaria present?

- Fever, rigors
- Jaundice
- Mental state ↓
- Diarrhoea
- Multi-organ failure

Malaria is a great mimicker

Influenza, typhoid, UTI, tick-bite fever, trypanosomiasis
Hepatitis
Meningitis
Travellers’ diarrhoea
Septicaemia
Pathophysiology of Clinical Malaria

1. Parasite Surface Antigens – PfEMP1
   - Parasite evades antibody-mediated killing via antigenic variation of PfEMP1
   - Parasite avoids splenic clearance with microvascular occlusion (“sticky” infected red blood cells-RBCs)
   - Organ specific inflammation

2. Parasite toxins
   - Released during schizont rupture in RBCs
   - Splenic inflammation and sepsis like symptoms

PfEMP1: P. falciparum erythrocyte membrane protein 1

How does malaria present?

• Fever may not be regular, may be initially irregular, or cyclic pattern may not be present in *P. falciparum*

• Cold-Hot-Sweating stages...

  - feeling of intense cold
  - vigorous shivering
  - lasts 15-60 minutes

  - intense heat
  - dry burning skin
  - throbbing headache
  - lasts 2-6 hours

  - profuse sweating
  - declining temperature
  - exhausted and weak → sleep
  - lasts 2-4 hours
**How does malaria present?**

**WHO Diagnostic Criteria for Severe Malaria**

- Cerebral malaria
- Generalised convulsions
- Severe normocytic anaemia
- Hypoglycaemia
- Metabolic acidosis
- Fluid and electrolyte disturbances
- Acute Renal Failure
- Acute pulmonary oedema and adult respiratory distress syndrome
- Circulatory collapse, shock, sepsicaemia
- Abnormal bleeding
- Jaundice
- Haemoglobinuria
- High fever
- Hyperparasitaemia
- Prostration
- Impairment of consciousness

**BOX 2: DISTINGUISHING FEATURES OF PLASMODIUM SPECIES**

<table>
<thead>
<tr>
<th></th>
<th>P. falciparum</th>
<th>P. vivax</th>
<th>P. ovale</th>
<th>P. malariae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>8 - 15</td>
<td>10 - 15</td>
<td>15</td>
<td>20 - 40</td>
</tr>
<tr>
<td>Periodicity of paroxysm</td>
<td>less than 48 (subtertian)</td>
<td>48 (tertian)</td>
<td>48 (tertian)</td>
<td>72 (quartan)</td>
</tr>
<tr>
<td>Stages seen in peripheral blood</td>
<td>rings and gametocytes</td>
<td>all stages</td>
<td>all stages</td>
<td>all stages</td>
</tr>
<tr>
<td>% of red blood cells infected</td>
<td>can be &gt; 50</td>
<td>2 - 3</td>
<td>2 - 3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Complicated malaria</td>
<td>common</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Course (years) of untreated cases</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>many</td>
</tr>
</tbody>
</table>

P. knowlesi: quotidian malaria (24 hrs) ~ Presents like P. falciparum; looks like P. malariae


- Multidrug-resistant *Plasmodium vivax* is widespread in eastern Indonesia, and emerging elsewhere in Asia-Pacific and South America, but *P. vivax* is generally regarded as a benign disease.
- Data were prospectively collected from all patients attending the outpatient and inpatient departments of the only hospital in the region using systematic data forms and hospital computerised records.

**Malaria Diagnosis**

- hinges on asking the patient if they have been travelling
- Malaria is a great mimicker
- If malaria is suspected, it should be regarded as a medical emergency until proven otherwise
- Blood films remain the “gold standard”
  - but needs trained technicians

**Not so “benign” malaria!!**

**Propensity of Patients with Severe Malaria**

<table>
<thead>
<tr>
<th>Age Group (Yrs)</th>
<th>Pure P. falciparum</th>
<th>P. vivax</th>
<th>P. ovale</th>
<th>P. malariae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 2</td>
<td>50</td>
<td>40</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>3 - 5</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>6 - 10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>11 - 15</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>16 - 20</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>21 - 50</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>51 - 70</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
</tr>
<tr>
<td>71+</td>
<td>0.313</td>
<td>0.313</td>
<td>0.313</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Source: [https://www.cdc.gov/dpdx/diagnosticProcedures/blood/antigendetection.html](https://www.cdc.gov/dpdx/diagnosticProcedures/blood/antigendetection.html)
What’s new in malaria treatment?

Therapeutic Guidelines: Antibiotic v15, 2014

- Options for treatment of uncomplicated malaria
  - Oral Artemether-lumefantrine (e.g. Riamet)
  - Oral Atovaquone+proguanil (e.g. Malarone)
  - Oral Quinine + doxycycline or clindamycin-child <8 yrs/pregnancy
  - (Mefloquine was removed in 2010)

- Those with *P. falciparum* and *P. knowlesi* should be initiated in hospital because of the small portion of patients who deteriorate after commencing therapy
  - Where artemisinin resistance suspected (persisting parasitaemia after 72 hours), which is reported in Greater Mekong Sub-region, switch to Quinine + doxycycline (or clindamycin)
  - Resistance being monitored, including by the Worldwide Antimalarial Resistance Network - WWARN
**What’s new in malaria treatment?**

**Therapeutic Guidelines: Antibiotic v15, 2014**

- **Options for treatment of relapse**
  - *P. vivax*: Primaquine 30 mg orally daily (or 15 mg q 12 h) for 14 days
  - *P. ovale*: Primaquine 15 mg orally daily for 14 days
  - Also effective in eliminating circulating gametocytes of *P. falciparum* malaria in areas where *Anopheles* mosquito present - Primaquine 15 mg orally daily for 14 days
- Primaquine can produce severe haemolysis in patients who are glucose-6-phosphate dehydrogenase (G6PD) deficient
  - Must exclude G6PD deficiency before giving primaquine

**What’s new in malaria treatment?**

- **Tafenoquine**
  - 8-aminoquinoline; primaquine analogue
  - Investigated for possible treatment and prevention of malaria
  - Long half life 2-3 weeks compared with 6 hours for primaquine
  - Single dose treatment could be an option
  - Like primaquine, G6PD remains a problem

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**What’s new in malaria prophylaxis?**

**Therapeutic Guidelines: Antibiotic v15, 2014**

- **Best options for malaria prophylaxis**
  - **Mefloquine**: 250mg weekly
  - **Doxycycline**: 100mg daily
  - **Atovaquone/Proguanil**: 250mg/150mg daily

- **Prophylaxis**
  - No changes
  - Main options: Atovaquone+proguanil, doxycycline & mefloquine
  - Taken for 4 weeks after leaving malarious area, except Atovaquone/proguanil, which is taken for 1 week at present (may change)

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**What’s new in malaria prophylaxis?**

**Therapeutic Guidelines: Antibiotic v15, 2014**

- **Mefloquine is not to be used in the Greater Mekong Sub-region**

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What’s new in malaria prophylaxis?

Therapeutic Guidelines: Antibiotic v15, 2014

- Stand-by emergency treatment (SBET)
  - Artemether+lumefantrine
  - Atovaquone+proguanil
  - Plus seek medical attention
- Mefloquine removed in 2010
- Atovaquone+proguanil is not to be used for treatment when used for prophylaxis

What else is used for prevention?

- Mosquito nets; treated nets more effective
- Mosquito coils
- Aerosol sprays
- Protective clothing
  - Consider thickness, treat with permethrin, loose fitting & footwear
- Screened windows, tight buildings, air-conditioning

Insect repellents
- DEET, IR3535 (EBAAP), Icaridin (Picaridin)

What does WHO recommend?

- Barrier/Area methods
- Insect repellents

Ref URL: http://www.who.int/ith/ (Section 3.7.4)

How effective are repellents?

- "Natural" products
  - Citriodiol™ or PMD
- Others, e.g.
  - Citronella oil
How do repellents work?

Stanczyk et al., 2015

• Repellents work on mosquitoes by directly stimulating avoidance behaviour or by blocking the mosquito’s receptors for attractive odours, not through toxicity.

Ref. Goodyer et al, 2010

Cx=Culex, Aa=Aedes, Ma=Mansonia, An=Anopheles

What are the pros and cons of repellents?

<table>
<thead>
<tr>
<th>Repellent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEET (N,N-diethyl-3-methylbenzamide)</td>
<td>Widely used and tested; effective; 20% protects for 5 hrs; good An &amp; against other biting arthropods</td>
<td>May damage fabrics &amp; plastics; toxicity concerns</td>
</tr>
<tr>
<td>IR3535 - ethylbutylacetamino-propionate (EBAAP)</td>
<td>Protects 7 h; good aesthetic properties; EPA-Biopesticide–alanine (amino acid); sandflies</td>
<td>Variation in efficacy</td>
</tr>
<tr>
<td>Icaridin or Picaridin (piperidine derivate);</td>
<td>Protects 5 h; 19.2% prep. similar protection to DEET; Less irritating than DEET</td>
<td>Inter-individual variation; 'activity against An</td>
</tr>
<tr>
<td>Citriodiol™ (made from Eucalyptus Citrus oil)</td>
<td>96% protection for up to 4 hours; plant based repellent, well tolerated; good for An</td>
<td>Inter-individual variation,</td>
</tr>
<tr>
<td>Natural oils - Citronella, Neem etc</td>
<td><em>Bio</em> - well accepted</td>
<td>Volatile; (very) short protection duration</td>
</tr>
</tbody>
</table>

Ref. Goodyer et al, 2010

Conclusions

• Malaria remains a significant disease.
• Progress is being made to contain malaria.
• Eradication is now being considered.
• There are five species of human malaria.
• Guidelines for treatment and prophylaxis has not changed greatly in the past 6 years.
• Drug resistance is increasing and combination drugs have become the norm.

Future-Malaria vaccines

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• Progress is being made to contain malaria.
• Eradication is now being considered.
• There are five species of human malaria.
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References 1

• Cox-Singh et al. CID 2008:146: 165-171
• Kuhel KL et al. KAF156 is an antimalarial clinical candidate with potential for use in prophylaxis. Antimicrobial Agents Chemotherapy AC 2014; 58: 5060-7
• Tang et al. Malaria Joura 2010; 9: 219
Personal protective measures


Questions

Glossary

- **Paroxysm**: Cyclic manifestation of acute illness in malaria, characterized by a rise in temperature with accompanying symptoms, usually caused by invasion of the blood by a brood of parasites released from RBC's.
- **Periodicity**: recurrence at regular intervals of symptoms in malaria, characterized clinically by paroxysms and resulting from the invasion of the blood by new generations of parasites. Periodicity may be quotidian, tertian, quartan or double quartan according to the intervals between paroxysms.
- **Relapse**: recurrence of parasitaemia with fresh infection of RBC's by merozoites derived from hypnozoites
- **Recrudescence**: renewed manifestation of infection due to survival of RBC's forms.
- **Prepatent period**: between sporozoite inoculation and the detection of parasites in the blood.
- **Incubation period**: time between infection and the appearance of symptoms.

http://www.tulane.edu/~wiser/protozoology/notes/malaria.html